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(71) Applicants *(for all designated States except US)*: UNIVERSITY OF BRISTOL [GB/GB]; Senate House, Tyndall Avenue, Bristol BS8 1TH (GB). TOCRIS COOKSON LIMITED [GB/GB]; Churchill Building, Langford House, Langford, Bristol BS18 2DY (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WATKINS, Jeffrey, Clifton [GB/GB]; 8 Lower Court Road, Lower Almondsbury, Bristol BS12 8DW (GB). JANE, David, Edward [GB/GB]; Flat 15, 35 Cotham Park, Cotham, Bristol, Bs6 5BY (GB).

(74) Agent: WILKINSON, Stephen, John; Stevens, Hewlett & Perkins, 1 St Augustine's Place, Bristol BS1 4UD (GB).

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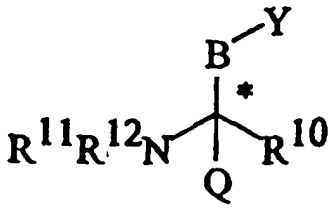
(54) Title: ALPHA-QUATERNARY-ALPHA-AMINO ACIDS FOR USE AS CNS AGENTS

(57) Abstract


(I)

Compounds of formula (I) are disclosed wherein: Y is selected from carboxy, phosphono, $-PO_2H(OR^{13})$, phosphinico, $-PO_2H(R^{13})$, $-OPO_3H_2$, $-OPO_2H(OR^{13})$, arsono, $-AsO_2H(OR^{13})$, arsinico, $-AsO_2H(R^{13})$, sulpho, sulphino, sulpheno, OSO_3H, tetrazolyl, 3-hydroxyisoxazole, 1,2,4-oxadiazolidin-3,5-dione and hydantoin where R^{13} is C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkylene or optionally substituted aryl or aralkyl; B is selected from C_1 to C_8 alkylene, C_3 to C_8 cycloalkylene, C_2 to C_8 alkenylene and C_2 to C_8 alkynylene optionally chain substituted and optionally substituted on the chain; Q is selected from carboxy, C_1 to C_6 alkoxycarbonyl and hydroxamic acid; R^{10} is selected from C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkylene, haloalkyl and optionally substituted aryl, aralkyl or biaryl; and R^{11} and R^{12} are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 acyl and optionally substituted benzoyl, two of Y, Q, R^{10}, R^{11}, R^{12} and the substituents on B being optionally condensed with each other to form a carbocyclic or heterocyclic ring system, and pharmaceutically acceptable salts thereof. The compounds may be used as agents to influence the central nervous system.

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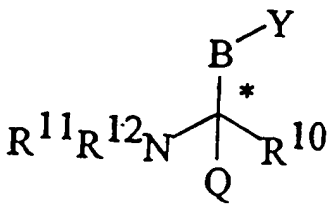
ALPHA-QUATERNARY-ALPHA-AMINO ACIDS FOR USE AS CNS AGENTS

This invention relates to novel α-substituted amino acids, their use as agents influencing the central nervous system (CNS), their preparation, their use as research tools and as pharmaceuticals, pharmaceutical compositions containing them and their use in the manufacture of medicaments for use in methods of treatment practised on the human or animal body.

Various amino acids have recently become of interest following the discovery that they are able to infuence the activity of certain receptor sites in the CNS and attention had been directed to the identification of material that will have specific action in relation to these receptor sites with a view to identifying compounds that can be used to control various involuntary muscular activity and/or mental and/or affective and/or memory disorders resulting from central nervous malfunction, and/or to control the perception of the sensation of pain.

We have found that certain α-alkyl or α-aryl substituted amino acids bearing a side chain containing an acidic functional group such as carboxy or phosphono have actions at certain amino acid receptor sites in the central nervous system which are involved in the control of the transmission of nerve impulses in the brain and spinal cord, including those underlying memory processes and the perception of pain.

Accordingly, the present invention provides compounds of the general formula I



wherein: Y is selected from carboxy, phosphono, $-PO_2H(OR^{13})$, phosphinico, $-PO_2H(R^{13})$, $-OPO_3H_2$, $-OPO_2H(OR^{13})$, arsono, $-AsO_2H(OR^{13})$, arsinico, $-AsO_2H(R^{13})$, sulpho, sulphino, sulpheno, $-OSO_3H$, tetrazolyl, 3-hydroxyisoxazole, 1,2,4-oxadiazolidin-3,5-dione and hydantoin where R^{13} is C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkylene or optionally substituted aryl or aralkyl;

B is selected from C_1 to C_8 alkylene, C_3 to C_8 cycloalkylene, C_2 to C_8 alkenylene and C_2 to C_8 alkynylene optionally chain substituted and optionally substituted on the chain;

Q is selected from carboxy, C_1 to C_6 alkoxycarbonyl and hydroxamic acid;

R^{10} is selected from C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkylene, haloalkyl (such as trifluoromethyl) and optionally substituted aryl, aralkyl or biaryl; and

R^{11} and R^{12} are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 acyl and optionally substituted benzoyl,

two of Y,Q, R^{10}, R^{11} and R^{12} and the substituents on B being optionally condensed with each other to form a carbocylic or heterocyclic ring system, and pharmaceutically acceptable salts thereof.

Optional chain substituents in B include one or more of N-H, N-C_1 to C_6 alkyl, N-C_2 to C_6 alkenyl, N-C_2 to C_6 alkynyl, N-C_1 to C_6 acyl, S, SO, SO_2, CO or O. Optional substituents on chain B and on the aromatic rings specified for Y R^{10}, R^{11} and R^{12} include one or more of C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halo, nitro, azido, hydroxy, cyano, ketoalkyl, ketoaryl, carboxy, alkoxycarbonyl, haloalkyl, sulpho, sulphoxide, sulphone, phosphono, tetrazolyl, tetrazolylalkyl, haloalkenyl, aryl or heteroaryl optionally substituted on the aromatic ring or rings by one or more halo, nitro or hydroxy groups,

C_1 to C_6 alkoxy, haloalkoxy, arylalkoxy and haloaralkoxy.

Preferably B is C_3 to C_8 cycloalkylene or C_1 to C_8 alkylene. Suitable cycloalkylene groups include 1,2-cyclopropylene, 1,2- or 1,3-cyclobutylene,1,2- or 1,3-cyclopentylene and 1,2-, 1,3- or 1,4-cyclohexylene.

Preferably, Y is carboxy, phosphono,-$PO_2H(OR^{13})$, phosphinico,-$PO_2H(R^{13})$,-OPO_3H_2 or -$OPO_2H(OR^{13})$ and it has been found that compounds with particularly effective activity are those in which Y is phosphono,-$PO_2H(OR^{13})$,-$OPO_2H(OR^{13})$ or -$AsO_2H(OR^{13})$. For synthetic reasons, Q is preferably carboxy, R^{10} is C_1 to C_6 alkyl or benzyl and R^{11} and R^{12} are both hydrogen.

The generic terms "alkyl", "alkenyl" and "alkynyl" as used herein include both straight chain and branched-chain alkyl groups. However, reference to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analagous convention applies to other generic terms.

The stereochemistry at asymmetric carbon atom C* in formula I may be in predominantly or substantially completely the (S) or (R) enantiomeric forms or may be a racemic mixture.

It is to be generally understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more substituents containing an asymmetric carbon atom, the invention includes any optically active or racemic form which may influence the activity of receptor sites in the CNS.

According to the present invention there is also provided the first pharmaceutical use of the compounds of formula I.

There is also provided the use of the compounds of formula I in the manufacture of a medicament for the treatment of disorders of the central nervous system.

Certain representatives of the compounds of the invention influence the CNS to enhance its electrical activity while others depress central nervous electrical activity. Substances of the invention which enhance the electrical activity of the CNS may directly activate or potentiate the activity of excitatory amino acid (EAA) receptors, particularly by interaction with one or more EAA receptors of the metabotropic type known as metabotropic glutamate receptors (mGluRs). Compounds which act at these receptors are useful as research tools for investigating mechanisms of central nervous function, and also, as an aid to the isolation and chemical characterization of excitatory amino acid receptors (for example, by incorporation into affinity chromatography support materials). These compounds may also be useful as therapeutic drugs to enhance electrical activity of the CNS in pathological conditions where such activity is depressed. Other examples depress the electrical activity of the central nervous system either by blocking post-synaptic EAA receptors or by activating presynaptic EAA receptors which mediate a reduction of synaptic excitatory activity. Substances of the application that block post-synaptic EAA receptors are useful as research tools for investigating central nervous mechanisms, and also as drugs for the treatment of disorders of the CNS due to hyperactivity of the CNS

(as in epilepsy and spasticity) and for the treatment of those neurodegenerative disorders of the CNS which are due to excessive activation of EAA receptors as is known to occur in ischaemic conditions such as those arising in stroke, heart failure, traumatic head or spinal injury, or which are due to ingestion of certain neurotoxic substances. Examples of substances with this depressant activity include those which block the N-methyl-D-aspartate type (NMDA)-type of EAA receptor as well as those that have antagonist action at non-NMDA receptors such as ∝-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) or kainate type. Examples of the compounds of the invention that depress central nervous activity by activating presynaptic metabotropic glutamate receptors are likewise useful as research tools for investigating mechanisms of CNS activity and as drugs for the treatment of disorders of the CNS which require a depression of the nervous system activity such as in epilepsy, spasticity and other conditions involving hyperactivity of the CNS in whole or in part.

The stereochemistry of the asymmetric carbon atom denoted * in formula I is important to the activity observed. Antagonism of the activity of post-synaptic NMDA receptors is seen most often in substances in which the stereochemistry is substantially completely of the R configuration. An agonist or antagonist action at metabotropic glutamate receptors of either a pre- or post-synaptic location is seen most often in compounds where the stereochemistry is of the S configuration. It is expected, however, that whether a substance is an agonist or antagonist at excitatory amino acid receptors will depend on several features of the

molecule simultaneously, as well as on the particular sub-type of excitatory amino acid receptor affected.

The groups R^{10}, R^{11}, R^{12} and any substituents in or on the chain B may be varied to alter the potency and/or the selectivity in the action of the substance at a particular type or sub-type of EAA receptor and also to affect the hydrophilic/lipophilic balance of the molecule in order to assist absorption from the gut and/or passage from the blood into the central nervous system.

The substituents on chain B may be groups which have an electron-withdrawing influence on the group Y so as to increase the acidity of this group and so enhance the ability of the substance to bind to EAA receptors. Thus, the substituents may be independently halogen, nitro, azido, hydroxy, cyano, ketoalkyl, ketoaryl, carboxy, alkoxycarbonyl, haloalkyl, sulpho, sulphoxide, sulphone, phosphono, tetrazolyl, tetrazolylalkyl, alkenyl, haloalkenyl, aryl, heteroaryl, haloaryl, nitroaryl, polynitroaryl, hydroxyaryl, polyhydroxyaryl, alkoxy, haloalkoxy, arylalkoxy or haloaralkoxy.

It is preferred that B is fully saturated or has some degree of unsaturation. The compounds may be radiolabelled and unsaturation in the B chain is particularly useful for the introduction of radioisotopes into the compounds.

For use as radioactive ligands for receptor binding and metabolic studies, radioactivity can be introduced as ^{125}I or another radioisotope of iodine in the B chain or the R^{10}, R^{11}, and R^{12} groups, or (particularly) as tritium, by hydrogenation using tritium of precursor molecules bearing unsaturation in any of the substituent groups or of unsaturation within the B chain or in ring systems, by

displacement of groups able to be hydrogenolized by ^{3}H, or displacement of ^{1}H in labile sites by ^{3}H.

It is envisaged that the substances will be useful also for the isolation of receptors from central nervous tissue, for example, by linking the molecules via a spacer molecular chain to an affinity chromatography support material of the sepharose or agarose type. In another embodiment, therefore, the invention provides the compounds bound to an affinity chromatography support, optionally via a spacer arm, for use in the isolation of receptors from central nervous tissue. This can be done by using one or more of the groups in the compounds as a reactive substituent for linking to the spacer arm, which would carry at its other end a group capable of reacting with sepharose, agarose, or like affinity chromatography support material.

The spacer arm may be substantially as used conventionally in the art, for example, it may be an alkyl, aryl or alkylaralkyl chain of from one to eight carbon atoms in length.

The compounds of the invention usually contain a centre of asymmetry. The compounds of the present invention include both RS mixtures, including racemic mixtures, and compounds in which the carbon atom bearing the BY, R^{10}, Q and $NR^{11}R^{12}$ substituents is substantially completely in the R configuration or substantially completely in the S configuration.

In another embodiment, the present invention provides a process for preparing a compound of formula I comprising the reaction of a compound of formula L-B-Y with a compound of formula R^{10}-A, wherein:

L is a leaving group;

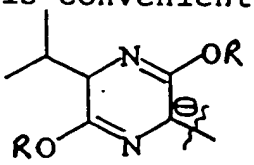
A is a synthetic equivalent of $\ominus C(NH_2)(COOH)$; and

B, Y and R^{10} are as defined above

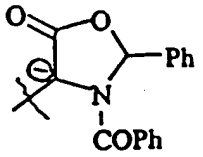
in a suitable solvent for the reaction.

Preferably, L is selected from halo, para-toluenesulphonyloxy, acetoxy, sulphate, methanesulphonyloxy and benzenesulphonyloxy.

A is conveniently one of the following:

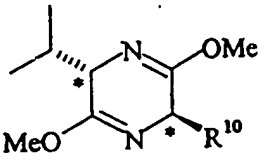


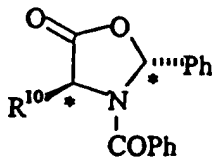
or



where R=C_1 to C_6 alkyl or benzyl

and R^{10}-A is typically provided as the anion of a metallic salt (such as a lithium, copper or lithium cuprate salt). In this way, the compounds of the invention may be formed stereoselectively as is well-known in the art by providing R^{10}-A as a chiral auxilliary such as the following:





The reaction may be carried out in anhydrous tetrahydrofuran, optionally with other solvents or co-solvents.

The adduct formed in the reaction of L-B-Y and R^{10}-A is optionally purified where desired or necessary, for example, by silica gel chromatography and is converted to a compound of the invention (deprotected) by acid hydrolysis for example by stirring in 1N trifluoroacetic acid in tetrahydrofuran or acetonitrile, followed by heating under reflux in 6N aqueous hydrochloric acid, and purification, for example, by ion-exchange chromatography and then

crystallisation from an appropriate solvent.

The invention also provides a process for preparing the compounds of the invention which comprises the reaction of a compound of formula (Y-B-)COR^{10} with a compound of formula $R^{11}R^{12}NH_2^+X^-$, wherein:

X is an anion; and

Y,B,R^{10},R^{11} and R^{12} are as defined above, in the presence of a cyanide salt (preferably sodium or potassium cyanide) in a suitable solvent for the reaction. The reaction may be the well-known Strecker Synthesis in which the solvent for the reaction is water/methanol or water/ammonia/methanol, X^- is the anion of a strong acid and the reaction is carried out at room temperature. Alternatively, the reaction may be the well-known Bucherer-Berg sythesis in which $R^{11}R^{12}NH_2^+X^-$ is ammonium carbonate and the reaction is carried out in the same solvents at 40 to 80°C, if necessary, under pressure. The reaction is followed where desired or necessary by purification, for example, by silica gel chromatography, deprotection, for example, in 6N aqueous hydrochloric acid, and purification for example, by ion-exchange chromatography and then crystallisation from an appropriate solvent.

Compounds of general formula I in which the carbon atom bearing the substituents BY, R^{10} and $NR^{11}R^{12}$ is substantially completely in the R or substantially completely in the S configuration can be prepared from the corresponding RS mixtures by classical resolution procedures preferably involving fractional crystallization of the salt formed with either R or S lysine or R or S arginine where applicable, however, other methods may be employed. Chiral HPLC may, for example, be used to separate racemates particularly where the compounds contain more than one chiral centre. Chiral centres may be present in other parts of compounds of general formula I and it is envisaged

that classical resolution procedures would also be useful for separating the resultant diastereoisomers.

Certain of the intermediates formed during the preparation of the compounds of formula I are novel, and are also provided. Those novel compounds include protected derivatives of the compounds of formula I.

When the compounds of the invention contain both basic and acidic functions either or both of the basic or acidic functions can be prepared in the compounds of the invention in salt form. Thus, for formulation reasons, it is often desirable to prepare an amino acid carboxylic acid residue and/or other acid residues present in the molecule in the form of a physiologically acceptable water-soluble salt such as the sodium salt. Compounds of the invention can also be prepared in the form of salts of the basic amino group present in the molecule and here, salts of interest are physiologically acceptable acid addition salts, such as salts with hydrochloric acid, acetic acid, succinic acid, tartaric acid, or citric acid.

In accordance with a further feature of the invention, we provide a pharmaceutical composition comprising a compound of formula I as defined above with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method for the treatment of a disorder of the central nervous system comprising the administration to a patient of the compounds or the compositions of the invention.

Compounds of the invention act on the central nervous system and may be administered parenterally or orally, for example, intravenously for acute treatment, or subcutaneously or orally for chronic treatment. Compounds of the invention may be

formulated for clinical use in suitable vehicles, normally as a preparation of a water-soluble salt, though preparations of low water solubility, possibly in association with physiologically tolerable emulsifying agents, may be used for depot administration.

Since it is believed to be necessary for compounds of the invention to penetrate the blood brain barrier, it is frequently necessary to administer the compounds of the present invention in amounts significantly in excess of the amounts necessary to be achieved within the brain for the therapeutic effect desired and this will influence the concentration of the active compounds in the composition of the present invention. Considerations of this type suggest that such a conventional dosage volume would provide the subject with up to about 200 mg/kg body weight although, when the compounds are to be administered by the intravenous route, dosages in the region of about 1-20 mg/kg body weight are to be expected for the more active compounds and/or for those substances with a high lipophilic or hydrophilic balance.

The compounds for use in the pharmaceutical compositions may be in the form of prodrugs, for example, so modified that they enter the body in a modified inactive form but are converted to their active form at or before a desired site of the body.

More specifically, compounds of the invention have been found to stimulate or antagonize EAA receptors and to stimulate or depress spontaneous and evoked synaptic activity in the central nervous system. Amino acid receptors mediate or modulate synaptic excitation and inhibition of many synapses in the brain. The compounds of the present invention

can modify abnormal central nervous system activity involving amino acid receptors and consequently are of interest in providing beneficial intervention in cases where such abnormalities arise.

The compounds of formula I have one or more of the following advantages. Most importantly, they are more potent and/or selective as either agonists or antagonists at metabotropic glutamate receptors than known compounds. Agonists at these receptors are known to facilitate synaptic plasticity mechanisms likely to be important in memory processes. Such compounds may be useful in cognitive enhancers. Antagonists at these receptors depress nociceptive responses and may then be useful as analgesics. Moreover, these substances constitute a group of compounds that are able to affect a greater variety of EAA receptors than known groups of compounds; they also have an improved lipophilic balance allowing for better absorbance at the blood/brain barrier, and they are more useful as research tools than known compounds of similar structure/function.

In particular, the compounds of formula I may provide insights into the existence and role in central nervous function of metabotropic glutamate receptor sub-types, as defined using molecular biology.

Example 1

Synthesis of
(2S,1'S,2'S)-2-Amino-2-(2'-carboxycycloprop-1'-yl)propanoic acid

Under a dry nitrogen atmosphere, (2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (1.5ml, 7.56mmol) was dissolved in THF

(10ml) and cooled to -78°C. A 2.5M solution of butyllithium in hexane (3.3ml, 8.32mmol) was injected slowly in to the reaction mixture, it was left to stir at this temperature for 40min. Methyl 4-bromobut-2-enoate (0.9ml, 7.56mmol) dissolved in THF (10ml) was injected into the solution at -78°C, it was maintained at this temperature and stirred overnight. Next day, the reaction mixture was allowed to warm up to room temperature. The solvent was removed in vacuo and the residue was partitioned between ether (100ml) and water (50ml), the aqueous layer was separated and was extracted with ether (2x50ml), the combined ether extracts were evaporated under reduced pressure to give a yellow oil. The oil was stirred in 1M trifluoroacetic acid in tetrahydrofuran (10ml) overnight. Next day the solvent was removed in vacuo and the residue was heated under reflux in 6M hydrochloric acid (25ml) overnight. The organic impurities were removed by extraction with diethyl ether (2x50ml). The aqueous layer was evaporated under reduced pressure and the residue was applied to an AG50 H^+ ion exchange resin column. Elution began with water (500ml) followed by 7% pyridine solution (500ml). The pyridine solution was evaporated under reduced pressure to give a white solid. The solid was dissolved in the minimum amount of water and neutralised to pH7 with AG1 hydroxide resin. This mixture was applied to an AG1 acetate ion exchange resin column. Elution began with water (500ml), followed by 0.01M, 0.02M, 0.03M, and 0.05M aqueous acetic acid . The ninhydrin positive fractions of the 0.05M acetic acid eluate were evaporated to dryness. The crude compound was then crystallised from water to give (2S,1'S,2'S)-2-Amino-2 -(2'-

carboxycycloprop-1'-yl)propanoic acid (0.507g, 38.7%) as a white solid.

Example 2

Synthesis of
(2S) 2-amino-2-methylhexan-1,6-dioic acid

Under a dry nitrogen atmosphere, (2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (0.5ml, 2.5mmol) was dissolved in THF (10ml) and cooled to -78°C. A 2.5M solution of butyllithium in hexane (1.05ml, 2.62mmol) was injected slowly in to the reaction mixture, and stirred at this temperature for 40min. The reaction mixture was added dropwise via a double tip needle to a solution of copper bromide methylsulphide complex (0.26g, 1.25mmol) in tetrahydrofuran (10ml) and dimethylsulphide (2ml) at -78°C. The mixture was warmed to -30°C to - 40°C and stirred for 30 min. 4-Bromobutanenitrile (0.25ml, 2.5mmol) in tetrahydrofuran (5ml) was then added at -78°C. The reaction mixture was allowed to stir overnight at -78°C. Next day, the reaction was warmed to room temperature. The solvent was removed in vacuo and the residue partitioned between ether (2x100ml) and water (100ml). The combined ether layer was evaporated under reduced pressure to give a residue which was dissolved in 1M trifluoroacetic acid in tetrahydrofuran (10ml) and stirred overnight. Next day, the solvent was remove in vacuo, and the oily residue was heated under reflux in 6M hydrochloric acid for 24 hr. The reaction mixture was evaporated to dryness and the solid was put through an AG50 H^+

ion exchange resin column. Elution began with water (500ml) followed by 7% pyridine solution (500ml). The pyridine solution was evaporated under reduced pressure to give an oil which was dissolved in the minimum amount of water and neutralised to pH7 with AG1 hydroxide resin. This mixture was placed on a AG1 acetate ion exchange resin column. Elution began with water (500ml), followed by 0.01M, 0.03M, 0.06M, and 0.1M aqueous acetic acid. Ninhydrin positive fractions of the 0.1M acetic acid eluate were evaporated to dryness. The crude compound was then crystallised from water to give 2-amino-2-methylhexan-1,6-dioic acid (67mg, 15.3%) as a white solid.

Example 3

Synthesis of
(2S)-2-Amino-2-methyl-4-phosphonobutanoic acid

Under a dry nitrogen atmosphere, (2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (1.5 ml, 7.6 mmol) was dissolved in dry tetrahydrofuran (15 ml) and cooled to -78°C. A 2.5M hexane solution of butyllithium (3.2 ml, 7.9 mmol) was injected into the reaction mixture at -78°C and allowed to stir for 0.5h. The mixture was then added dropwise via a double tipped needle to a solution of copper bromide-methyl sulphide complex (0.78g, 3.8 mmol) in dry tetrahydrofuran (15 ml) and dimethyl sulphide (3 ml) at -78°C. The solution was warmed to -40°C and stirred for 0.5h. Diethyl 2-bromoethylphosphonate (1.38 ml, 7.6 mmol) dissolved in tetrahydrofuran (8 ml) was injected into the reaction mixture at -78°C. The solution was allowed to stir

at -78°C for 15-16h at -78°C and then allowed to warm to room temperature. The solvent was removed in vacuo and the residue partitioned between water (100 ml) and diethyl ether (100 ml), the aqueous layer was then extracted with diethyl ether (2x50 ml) and the combined extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in a 1M solution of trifluoroacetic acid in tetrahydrofuran (10ml) and stirred overnight. Next day, the solvent was removed to leave an oil which was heated under reflux in concentrated hydrobromic acid (50 ml) for 48h. The mixture was evaporated to leave an oil which was dissolved in the minimum amount of water and neutralised to pH7 with AG1 hydroxide resin. This mixture was placed on an AG1 acetate ion exchange resin column. Elution began with water (500ml), followed by 0.01M (500 ml), 0.05M (500 ml), 0.1M (500 ml), and 0.5M (500 ml) aqueous acetic acid. Ninhydrin positive fractions of the 0.5M aqueous acetic acid eluate were evaporated to dryness to give a yellow oil. Crystallisation was achieved by dissolving the oil in the minimum amount of water and slowly dropping the resultant solution into vigorously stirred absolute alcohol. The solid was filtered under a dry nitrogen atmosphere and washed with anhydrous ether. It gave (2S)-2-amino-2-methyl-4-phosphonobutanoic acid as a white solid (0.586g, 39%).

Example 4

Synthesis of
(2S) 2-amino-2-methylheptan-1,7-dioic acid

Under a dry nitrogen atmosphere,

(2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (0.5 ml, 2.5 mmol) was dissolved in THF (10 ml) and cooled to -78°C. A 2.5M solution of butyllithium in hexane (1.05 ml, 2.6 mmol) was injected slowly in to the reaction mixture, and stirred at this temperature for 40min. The reaction mixture was added dropwise via a double tip needle to a solution of copper bromide methylsulphide complex (0.26g, 1.25 mmol) in tetrahydrofuran (10 ml) and dimethylsulphide (2 ml) at -78°C. The mixture was warmed to -30°C to -40°C and stirred for 30 min. methyl 5-Bromopentanoate (0.54 ml, 3.75 mmol) in tetrahydrofuran (5 ml) was then added at -78°C. The reaction mixture was allowed to stir overnight at -78°C. Next day, the reaction was warmed to room temperature. The solvent was removed in vacuo and the residue partitioned between ether (2x100ml) and water (100ml). The combined ether layer was evaporated under reduced pressure to give a residue which was dissolved in 1M trifluoroacetic acid in tetrahydrofuran (10 ml) and stirred overnight. Next day, the solvent was remove in vacuo, and the oily residue was heated under reflux in 6M hydrochloric acid for 24 hr. The reaction mixture was evaporated to dryness and the solid was put through an AG50 H^+ ion exchange resin column. Elution began with water (500ml) followed by 7% pyridine solution (500ml). The pyridine solution was evaporated under reduced pressure to give an oil which was dissolved in the minimum amount of water and neutralised to pH7 with AG1 hydroxide resin. This mixture was placed on a AG1 acetate ion exchange resin column. Elution began with water (500ml), followed by 0.01M, 0.03M and 0.05M aqueous acetic acid. Ninhydrin positive fractions of the 0.05M acetic acid eluate were evaporated to

dryness. The crude compound was then crystallised from water to give (2S) 2-amino-2-methylheptan-1,7-dioic acid (0.15g, 32%) as a white solid.

Example 5

Synthesis of

(RS)- -Methyl serine O-phosphate and (RS)- ∝-Methyl serine O-phosphate monophenyl ester

A mixture of (RS)-2-(Benzyloxycarbonylamino)-2-(hydroxymethyl)propanoic acid (10g, 0.04 mol), p-toluenesulphonic acid (0.5g) and benzyl alcohol (20 ml, 0.193 mol) in tetrachloromethane (100 ml) was heated under reflux in a Dean-Stark apparatus until removal of water was complete. The solution was cooled, washed with a 20% aqueous solution of sodium hydrogen carbonate (2x50 ml) and water (3x50 ml). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash silica gel chromatography. Elution with ethyl acetate/petroleum ether (20:80) gave (RS)-benzyl 2-(benzyloxycarbonylamino)-2-(hydroxymethyl)propionate (9.6g) as a pale yellow oil.

To (RS)-benzyl 2-(benzyloxycarbonylamino-2-(hydroxymethyl)propionate (1.93g, 5.63 mmol) dissolved in anhydrous pyridine (10 ml) and cooled to 10°C, was added diphenyl chlorophosphate (1.4 ml, 6.75 mmol) slowly over a period of 10 min. keeping the temperature below 40°C. Stirring was continued overnight at room temperature. Next day, water (0.5 ml) was added to the solution and the mixture was stirred for 1h. The reaction mixture was poured into a mixture of ice-water (100 ml) and ether (100 ml).

The organic layer was separated and washed with 4M aqueous sulphuric acid (2x50 ml), water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (100 ml). The ether layer was dried ($MgSO_4$) and evaporated in vacuo. It gave benzyl (RS)-benzyl 2-(benzyloxycarbonylamino)-2-(diphenylphosphonyloxy)propionate (3.24g) as a clear oil. A mixture of benzyl (RS)-benzyl 2-(benzyloxycarbonylamino)- 2- (diphenylphosphonyloxy) propionate (3.24g) and 10% palladium on carbon (0.8g) in absolute ethanol (100 ml) was stirred under a hydrogen atmosphere until hydrogen uptake was complete. A warm mixture of water (50 ml) and acetic acid (50 ml) was added to the mixture, the resulting suspension filtered through a bed of celite and the celite washed with hot water (100 ml). The combined filtrates were evaporated under reduced pressure. The solid residue was taken up in acetic acid (50 ml) and water (10 ml), platinum dioxide (0.5g) was added and the mixture stirred under an atmosphere of hydrogen for 16h. The mixture was filtered through a bed of celite and the filtrate was evaporated under reduced pressure. Crystallisation of the crude product from water gave (RS)-α-methyl serine O-phosphate mono phenyl ester (1.4g, 90%) as a white solid.

(RS)-α-methyl serine O-phosphate mono phenyl ester (1.4g, 5.1 mmol) was dissolved in water (10 ml) and acetic acid (50 ml), platinum dioxide (0.5g) was added and the mixture stirred under an atmosphere of hydrogen for 20h. Crystallisation of the crude solid from water gave (RS)-α-methyl serine O-phosphate (0.96g, 95%) as a white solid.

Example 6

Synthesis of

(S)-2-Amino-2-methyl-4-(phenylphosphino)butanoic acid

Diethyl phenylphosphonite (5g, 25 mmol) was dissolved in 1,2-dibromoethane (21.7 ml, 0.252 mol). The stirred mixture was heated to 150°C and the bromoethane so produced removed using a Dean-Stark apparatus. After bromoethane evolution had ceased excess 1,2-dibromoethane was removed by distillation under reduced pressure to leave ethyl 2-(bromoethyl)phenylphosphinate (6.46g, 92%) as an oil.

To a stirred solution of (2R,5S)-(-)-2,5-dihydro-3.6-diethoxy-2-isopropyl-5-methylpyrazine (2g, 8.84 mmol) in anhydrous THF (10 ml) at -78°C, under a dry nitrogen atmosphere, was added t-BuLi (5.7 ml, 9.7 mmol) over a period of 20 min. Stirring was continued at -78°C for 20 min. A solution of ethyl 2-(bromoethyl)phenylphosphinate (2.44g, 8.84 mmol) in dry THF (5 ml) was added and the mixture stirred at -78°C overnight. Next day, the solvent was removed under reduced pressure, the residue treated with a 1M solution of TFA in dry THF (10 ml) and the resulting solution allowed to stand overnight. Next day, the solvent was removed under reduced pressure, 6M aqueous HCl was added to the residue and the mixture heated under reflux overnight. The solution was cooled and extracted with ether (4x60 ml). The aqueous layer was separated and evaporated under reduced pressure. The residue was dissolved in water and applied to a bed of AG 50H$^+$ion exchange resin. Elution with water (500 ml) and evaporation of the ninhydrin positive fractions gave a yellow-brown solid. The solid was dissolved in water (10 ml), the solution brought to pH

6-7 with 1N aqueous sodium hydroxide and then applied to an AG1 acetate ion exchange resin column. Elution with water 0.01M acetic acid (200 ml), 0.05M acetic acid (100 ml), 0.1M acetic acid (100 ml), 0.5M acetic acid (100 ml), 1M acetic acid (500 ml) and evaporation of the ninhydrin positive fractions of the 1M acetic acid eluate gave a pale yellow solid. Crystallisation of the residue from water gave (S)-2-Amino 2-methyl-4-(phenylphosphino)butanoic acid (0.799g, 35%) as a white solid.

Example 7

Synthesis of (2R,5S)-(+)-2,5-Dihydro-3,6-diethoxy-2-isopropyl-5-benzyl-1,4-pyrazine

To a solution of (2R)-(+)-2,5-Dihydro-3,6-diethoxy-2-isopropyl-1,4-pyrazine (1g, 4.7 mmol) in THF (10 ml), under a dry nitrogen atmosphere, was added a 2.5 M solution of n-butyl lithium in hexane (1.96 ml, 4.9 mmol) at -78°C and the mixture stirred for 10-15 min. Benzyl bromide (0.56 ml) in dry THF (5 ml) was added and the mixture stirred overnight at -78°C. After allowing the mixture to warm to room temperature the solvent was removed in vacuo and the crude product was flash chromatographed over silica gel. Elution with ether/petroleum ether 5/95 gave (2R,5S)-(+)-2,5-Dihydro-3,6-diethoxy-2-isopropyl-5-benzyl-1,4-pyrazine (0.81g, 57%) as a pale yellow oil.

Synthesis of (R)-2-amino-2-benzyl-4-phosphonic acid

To a solution of (2R,5S)-(+)-2,5-Dihydro-3,6-diethoxy-2-isopropyl-5-benzyl-1,4-pyrazine (1g,

3.3mmol) in dry THF (10 ml), under a dry nitrogen atmosphere was added a 1.7M solution of t-butyl lithium in hexane (1.95 ml, 3.3 mmol) at -78°C and the mixture stirred for 30 min. Diethyl 2-bromoethylphosphonate (0.6 ml, 3.3 mmol) in dry THF (5 ml) was added and the mixture stirred overnight at -78°C. After allowing the mixture to warm to room temperature the solvent was removed in vacuo and the crude product treated with a 1M solution of trifluoroacetic acid in dry THF (10 ml) and the mixture allowed to stand overnight. Next day, the solvent was evaporated under reduced pressure, 6M aqueous HCl was added to the residue and the mixture heated under reflux overnight. Next day, the aqueous solution was extracted with ether (5x60 ml). The aqueous layer was separated and evaporated under reduced pressure. The residue was dissolved in water and applied to a bed of AG50H$^+$ ion exchange resin. Elution with water (500 ml), followed by aqueous pyridine (500 ml) and evaporation of the ninhydrin positive fractions of the aqueous pyridine eluate gave a brown-yellow oil. The residue was dissolved in water (10 ml) and applied to a bed of AG1 acetate ion exchange resin. Elution with water (200 ml), followed by 0.01M acetic acid (200 ml), 0.05M acetic acid (200 ml), 0.5M acetic acid (200 ml), 2M acetic acid and evaporation of the ninhydrin positive fractions of the 2M acetic acid eluate gave a pale yellow solid. Crystallization from water gave (R)-2-amino-2-benzyl-4-phosphonic acid (0.252g, 28%) as a white solid. It should be noted that in this example the (2R,5S) form of the Schollkopf reagent exceptionally gives the R amino acid instead of the usual S amino acid.

The compounds of the invention have agonist, partial agonist or antagonist action at excitatory amino acid receptors in the central nervous system. There are several types of these receptors, some or

all of which are intimately involved in central nervous function. Three types of ionotropic excitatory amino acid receptors that have been described in the neuroscientific literature are known as N-methyl-D-aspartate (NMDA), kainate (K) and -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and other types of excitatory amino acid receptors are also known, including metabotropic glutamate receptors. The NMDA, K and AMPA receptors, when activated, produce electrochemical changes in neurones which are important in transmission and metabotropic glutamate receptors additionally cause metabolic changes which are important in longer term changes in receptor function. Additionally, recent advances in molecular biology have revealed the existence of sub-types of the main groups of excitatory amino acid receptors described.

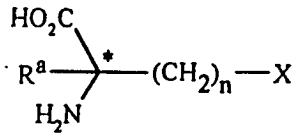
The compounds of the invention have differential actions at these amino acid receptors. Compounds which act at amino acid receptors can affect the action of natural amino acid transmitter substances and thereby influence the electrical activity of the central nervous system.

To evaluate the action of substances at amino acid receptors on nerve cells (neurones), the substances may be tested on spinal cord neurones, which have similar characteristics to nerve cells in the brain. Typically, the isolated spinal cord of the 1-5 day old rat is used, and compounds are tested for their ability to affect the activity of spinal neurones induced by amino acids or electrical stimulation of afferent fibres. The spinal cord is surgically removed from an anaesthetised rat and is longitudinally hemisected. A dorsal root is placed across a stimulating electrode and a ventral root

across a recording electrode. Recordings are made of the depolarization of motoneurones that are generated either by stimulating the corresponding dorsal root or by the action of excitatory amino acids (EAAs) added to the artificial physiological medium used to bathe the spinal cord. NMDA, kainate or AMPA may be used as the standard agonists for ionotropic EAA receptors of the NMDA, K, or AMPA types, and (1S,3R)-1-aminocyclopentane-1,3-dicarboxylate (ACPD) may be used as a standard agonist for a depolarizing type of metabotropic EAA receptor. L-2-Amino-4-phosphonobutyrate (L-AP4), (1S,3R)-ACPD, (1S,3S)-ACPD and (2S,3S,4S)- -(carboxycyclopropyl)glycine (L-CCG-I) may be used as standard agonists for one or more type(s) of metabotropic EAA receptor which mediates depression of monosynaptic excitation of motoneurones following dorsal root stimulation. The ability of substances to antagonize motoneuronal depolarization induced by excitatory amino acids or to antagonize the depression of monosynaptic excitation of motoneurones induced by L-AP4 or by (1S,3R)-ACPD, ((1S,3S)-ACPD or L-CCG-I) can be assessed by measuring the IC_{50} values of the substances producing such antagonism. Tables 5 and 7 show the activity of some invention compounds on motoneurones of the neonatal rat spinal cord.

It has been shown that some substances that interact with sub-types of metabotropic glutamate receptors which are coupled to the activity of adenylcyclase may antagonize the ability of agonists of these receptors to depress cyclic adenosine monophosphate (cyclic AMP) synthesis. Accordingly we show that certain examples of the invention antagonize the ability of L-2-amino-4-phosphonobutyrate (L-AP4) and L-CCG-I to depress forskolin-stimulated cyclic AMP production in rat cerebral cortical tissue (Table 6).

TABLE 1 Melting Points, Specific Rotations and Elemental Analytical Data for α-Methyl amino acids.
General Formula:



No.	R^a	n	X	Stereo (*)	m.p./°C	$^{20}[\alpha]_{589}$	$^{20}[\alpha]_{546}$	Calc (%) C	Calc (%) H	Calc (%) N	Found (%) C	Found (%) H	Found (%) N
1	Me	2	PO_3H_2	S	199.1-201.8	+7.54[1]	+8.46[1]	30.57[2]	6.80	6.37	30.35	6.96	5.86
2	Me	2	PO_3H_2	R	200-202	-7.22[7]	-6.62[7]	32.47[20]	7.09	6.11	32.46	7.16	6.25
3	Me	3	CO_2H	S	155.2-155.6	+8.89[3]	+8.89[3]	46.78[4]	7.59	7.80	46.48	8.02	7.90
4	Me	4	CO_2H	S	238.9-239.2	+11.3[5]	+13.9[5]	50.77[6]	8.01	7.40	50.33	8.26	7.54
5	Me	5	CO_2H	S	238.2-238.6	+11.7[8]	+14.4[8]	50.92	8.56	6.60	50.90	8.76	6.61
6	Me	1	PO_3H_2	RS	248.5-249.1 (dec)			26.23	5.52	7.65	26.15	5.72	7.59
7	Me	3	PO_3H_2	S	235.1-236.5 (dec)	+8.0[9]	+9.6[9]	34.12	6.70	6.63	33.86	7.09	6.34
8	Me	2	SO_3H	S	235-237 (dec)	+8.0[10]	+10.0[10]	25.74[11]	6.49	6.01	25.64	6.51	5.98

9	Me	1	OPO_3H_2	RS	210-212.2 (dec)			24.13	5.07	7.04	24.08	5.50	7.18
10	Me	1	OPO(OPh)OH	RS	220.9-222.6 (dec)			43.80	5.16	5.12	43.56	5.38	5.12
11	Me	2	PO(Ph)OH	S	178.2-178.6	+12.31[18]	+14.77[18]	49.28[19]	6.48	5.23	49.31	6.57	5.07
12	Et	2	CO_2H	S	165.1-165.2	+2.59[15]	+3.45[15]	47.49[14]	7.53	7.91	47.51	7.60	7.85
13	Benzyl	2	PO_3H_2	R	212.7-213.6 (dec)	-7.66[16]	-8.62[16]	46.80[17]	6.08	4.96	46.88	6.00	4.82
14	Et	2	PO_3H_2	S	230 5-232.1	+6.91[12]	+9.49[12]	33.41[13]	6.79	6.50	33.47	7.22	6.56
15	Me	2	$PO(OH)(C_6H_{11})$	S	166.1-167 (dec)	+9.20[21]	+11.95[21]						
16	Benzyl	2	CO_2H	S	178.9-179.1	+4.10[23]	+6.15[23]						
17	Benzyl	2	PO_3H_2	S	212 2-212.9 (dec)			47.87[22]	6.00	5.08	48.12	6.49	5.08

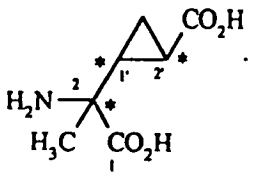
1) c = 0.43, H_2O.
2) Calculated for $C_5H_{12}NO_5P$. 0.3 C_2H_5OH. 0.5 H_2O..
3) c = 0.09, H_2O
4) Calculated for $C_7H_{13}NO_4$. 0.25 H_2O.
5) c = 0.23, 6M HCl.
6) Calculated for $C_8H_{15}NO_4$
7) c = 0.43, H_2O
8) c = 0.375, 6M HCl
9) c = 0.25, 6M HCl
10) c = 0.3, 6M HCl
11) Calculated for $C_5H_{11}NO_5S$. 2.05 H_2O
12) c = 0.463, 6M HCl

13) Calculated for $C_6H_{14}NO_5P$. 0.25 H_2O
15) c = 2.32, 6M HCl
17) Calculated for $C_{11}H_{16}NO_5P$. 0.5 H_2O
19) Calculated for $C_{11}H_{16}NO_4P$. 0.6 H_2O
21) c=0.22, 6M HCl
23) c=0.195, 6M HCl

14) Calculated for $C_7H_{13}NO_4$. 0.1 H_2O.
16) c = 0.4175, 6M HCl
18) c = 0.4875, 6M HCl
20) Calculated for $C_5H_{12}NO_5P$. 0.25 H_2O. 0.6 EtOH
22) Calculated for $C_{11}H_{16}NO_5P$. 0.15 H_2O

TABLE 2 Melting Points, Specific Rotations and Elemental Analytical Data for α-Methyl cyclopropyl amino acids.

General Formula:



No,	Stereo (*)	m.p./°C	$^{20}[\alpha]_{589}$	$^{20}[\alpha]_{546}$	Calc. (%) C	H	N	Found (%) C	H	N
18	2S,1'S,2'S[1]	235-239 (dec)	-55.5[3]	-65.88[3]	48.54[4]	6.41	8.09	48.21	6.60	8.11
19	2R,1'R,2'R[2]	232.8-233.4	+30.54[5]	+40.73[5]	42.10	7.06	6.92	42.39	6.47	6.90

1) Ratio of 2S,1'S,2'S : 2S,1'R,2'R is 95:5 (as measured by ^1H nmr).
2) Ratio of 2R,1'R,2'R : 2R,1'S,2'S is 88.5:11.5 (as measured by ^1H nmr).
3) c = 0.2125, H_2O.
4) Calculated for $C_7H_{11}NO_4$ .1.5 H_2O. 0.05 EtOH.
5) c = 0.2125, H_2O

TABLE 3 270 MHz ^{1}H NMR Data for Invention Compounds.

Compound	Solvent	Chemical Shifts (δ/ppm)
1	D_2O	2.0-2.3 (m, 3H), 1.7-1.9 (m, 2H), 1.6 (s, 3H)
2	D_2O	2.0-2.3 (m, 3H), 1.7-1.9 (m, 2H), 1.6 (s, 3H)
3	D_2O	2.35-2.5 (dt, 2H), 1.8-2.0 (m, 4H), 1.5 (s, 3H)
4	D_2O	2.2 (t, 2H), 1.65-2.0 (m, 4H), 1.49 (s, 3H), 1.2-1.5 (m, 2H)
5	D_2O	2.4 (t, 2H), 1.2-2.0 (m, 8H), 1.5 (s, 3H)
6	D_2O/NaOD	1.6-2.0 (ABX, 2H), 1.4 (s, 3H)
7	D_2O	1.9-2.1 (m, 2H), 1.4-1.8 (m, 4H), 1.6 (s, 3H)
8	D_2O	2.7-3.2 (m, 2H), 2.3-2.5 (m, 2H), 1.6 (s, 3H)
9	D_2O	4.0-4.3 (ABX, 2H), 1.6 (s, 3H)
10	D_2O	7.15-7.4 (m, 5H), 4.1-4.4 (ABX, 2H), 1.6 (s, 3H)
11	D_2O	7.5-7.7 (m, 5H), 1.7-2.0 (m, 4H), 1.5 (s, 3H)
12	D_2O	2.4-2.6 (m, 2H), 2.0-2.2 (m, 2H), 1.8-2.0 (m, 2H), 0.97 (t, 3H)
13	D_2O	7.3-7.4 (m, 5H), 3,27 (ABX, 2H), 2.0-2.4 (m, 2H), 1.5-2.0 (m, 2H)

14	D_2O	1.5-2.25 (M, 6H), 1.0 (t, 3H)
17	D_2O	7.3-7.4 (m, 5H), 3,27 (ABX, 2H), 2.0-2.4 (m, 2H), 1.5-2.0 (m, 2H)
18	D_2O	1.76-1.88 (m, 2H), 1.44 (s, 3H), 1.2-1.3 (t, 2H)
19	D_2O	1.76-1.88 (m, 2H), 1.44 (s, 3H), 1.2-1.3 (t, 2H)

TABLE 4 270 MHz ^{13}C NMR Data for Invention Compounds.

Compound	Solvent	Chemical Shifts (δ/ppm)
1	D_2O	171.53, 54.51, 28.22, 18.69, 13.84
2	D_2O	171.53, 54.51, 28.22, 18.69, 13.84
3	D_2O	175.38, 173.63, 58.15, 30.8, 33.59, 19.46, 16.13
4	D_2O	180.2, 174.2, 58.71, 34.07, 33.88, 22.7, 20.23, 19.59
5	D_2O	182.18, 179.61, 64.24, 39.71, 36.58, 30.84, 26.71, 25.6, 25.18
6	D_2O	187.29, 59.7, (d, 42.97, 41.71), 28.15
7	D_2O	177.66, (d, 40.7, 40 44), 28.79, 24.6, 20.22
8	D_2O	176.05, 63.91, 49.98, 35.25, 24.26
9	D_2O	175.19, 69.98, 63.15, 20.8
10	D_2O	175.19, 154.2, 132.58, 126.42, 122.8, 70.9, 63.16, 18.35

11	D_2O	176.81, 137.6, 135.73. 134.46, 133.44, 131.44, 63.21, 33.11, (d, 28.7, 27.31), 24.26
12	D_2O	179.91, 177.69, 67.65, 33.46, 31.84, 9.97
13	D_2O	175.82, 135.81, 132.83, 131.88, 130.92, 67.78, 44.03, 32.83, (d, 25.87, 23.9)
14	D_2O	176.45, 67.47, 32.38, 31.44, 25.44, 24.11
18	D_2O	174.55, 171.31, 57.82, 24.01, 16.89, 15.08, 8.8
19	D_2O	174.55, 171.31, 57.82, 24.01, 16.89, 15.08, 8.8

Table 5 Antagonism by α-alkyl amino acids of L-AP4-, (1S,3S)-ACPD- and L-CCG-I-induced depression of monosynaptic excitation of neonatal rat motoneurones (see Jane *et al.*, 1994)

Compound No	K_D (μM) for antagonism of depression mediated by		
	L-AP4	(1S,3S)-ACPD	L-CCG-I
1	22±5(5)	>500	>500
18	>500	103±28(5)	259±34(5)

Table 6 Antagonism by α-alkyl amino acids of the depression of forskolin-stimulated cyclic AMP formation effected by L-AP4 or L-CCG-I

Compound No	IC_{50} (nM) for antagonism of the depression of forskolin-stimulated cyclic AMP formation effected by	
	L-AP4	L-CCG-I
3	80	30

Table 7 Antagonism by α-alkyl amino acids of L-AP4- and (1S,3S)-ACPD-induced depression of monosynaptic excitation of neonatal rat motoneurones.

COMPOUND	RELATIVE POTENCY[1] VERSUS	
	L-AP4	(1S,3S)-ACPD
9	0.80	2.30
10	1.00	0.50

1) Relative potencies for α-methyl serine-O-phosphate derivatives, where the known metabotropic glutamate antagonist, (±)-α-methyl-4-carboxyphenylglycine (see Kemp *et al.*, 1994)= 1, and the smaller the value, the more potent the compound. All antagonists were screened at 200μM.

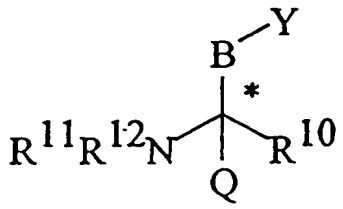
REFERENCES

Kemp, M., Roberts, P. J., Pook, P. C-K., Jane, D. E., Jones, A. W., Jones, P. L. St-John, Sunter, D. C., Udvarhelyi, P. M. and Watkins, J. C. (1994) Antagonism of presynaptically mediated depressant responses and cyclic AMP-coupled metabotropic glutamate receptors. Eur.J.Pharmacol.-Molec. Pharm. Sect., **266**, 187-192

Jane, D. E., Jones, P. L. St-John, Pook, P. C-K., Tse H-W and Watkins, J. C. (1994) Actions of two new antagonists showing selectivity for different sub-types of metabotropic glutamate receptor in the neonatal rat spinal cord. Br.J.Pharmacol., **112**, 809-816.

CLAIMS

1. Compound of formula I



I

wherein: Y is selected from carboxy, phosphono, $-PO_2H(OR^{13})$, phosphinico, $-PO_2H(R^{13})$, $-OPO_3H_2$, $-OPO_2H(OR^{13})$, arsono, $-AsO_2H(OR^{13})$, arsinico, $-AsO_2H(R^{13})$, sulpho, sulphino, sulpheno, OSO_3H, tetrazolyl, 3-hydroxyisoxazole, 1,2,4-oxadiazolidin-3,5-dione and hydantoin where R^{13} is C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl or optionally substituted aryl or aralkyl;

B is selected from C_1 to C_8 alkylene, C_3 to C_8 cycloalkylene, C_2 to C_8 alkenylene and C_2 to C_8 alkynylene optionally chain substituted and optionally substituted on the chain;

Q is selected from carboxy, C_1 to C_6 alkoxycarbonyl and hydroxamic acid;

R^{10} is selected from C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl , haloalkyl and optionally substituted aryl,aralkyl or biaryl; and

R^{11} and R^{12} are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, C_1 to C_6 acyl and optionally substituted benzoyl,

two of Y, Q, R^{10}, R^{11}, R^{12} and the substituents on B being optionally condensed with each other to form a carbocyclic or heterocyclic ring system, and pharmaceutically acceptable salts thereof.

2. Compound as claimed in claim 1, wherein B is C_1 to C_8 alkylene or C_3 to C_8 cycloalkylene.

3. Compound as claimed in claim 1, or claim 2, wherein Y is carboxy, phosphono, $-PO_2H(OR^{13})$, phosphinico, $-PO_2H(R^{13})$, $-OPO_3H_2$ or $-OPO_2H(OR^{13})$.

4. Compound as claimed in claim 1 or claim 2 wherein Y is phosphono, $-PO_2H(OR^{13})$, $-OPO_2H(OR^{13})$ or $AsO_2H(OR^{13})$.

5. Compound as claimed in any one of claims 1 to 4, wherein Q is carboxy.

6. Compound as claimed in any one of claims 1 to 5, wherein R^{10} is C_1 to C_6 alkyl, or benzyl.

7. Compound as claimed in any one of claims 1 to 6, wherein R^{11} and R^{12} are both hydrogen.

8. Compound as claimed in any one of claims 1 to 7, which is radiolabelled.

9. Compound as claimed in claim 8, wherein the radiolabelling comprises substitution of a hydrogen atom by tritium or a radioisotope of iodine.

10. Compound as claimed in any one of claims 1 to 9 bound to an affinity chromatography support, optionally via a spacer arm, for use in the isolation of receptors from central nervous tissue.

11. Pharmaceutical composition comprising a compound of any one of claims 1 to 7 and a pharmaceutically acceptable diluent or carrier.

12. Process for preparing a compound of formula I, as defined in claim 1, comprising the reaction of a compound of formula L-B-Y with a compound of formula R^{10}-A,

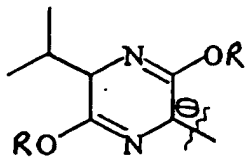
L is a leaving group;

A is a synthetic equivalent of $\ominus C(NH_2)(COOH)$; and

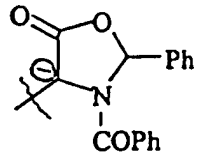
B, Y and R^{10} are as defined in claim 1, in a suitable solvent for the reaction.

13. Process as claimed in claim 12, wherein L is selected from halo, para-toluenesulphonyloxy, acetoxy, sulphate, methanesulphonyloxy and benzenesulphonyloxy.

14. Process as claimed in claim 13, wherein A is



or



formed by

where R=C_1 to C_6 alkyl or benzyl

deprotonation of the corresponding protonated compounds.

15. Process as claimed in claim 14, wherein the adduct formed by the reaction of L-B-Y and R^{10}-A is optionally purified and subjected to acid hydrolysis to form the compound of formula I.

16. Process for preparing a compound of formula I, as defined in claim 1, comprising the reaction of a compound of formula (Y-B-)COR^{10} with a compound of formula $R^{11}R^{12}NH_2^+X^-$, wherein:

X is an anion; and

Y,B,R^{10},R^{11} and R^{12} are as defined in claim 1, in the presence of a cyanide salt in a suitable solvent for the reaction.

PCT/GB 94/02690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/24 C07F9/38 C07F9/09 C07F9/30 A61K31/195 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOCHEMISTRY (BICHAW,00062960);85; VOL.24 (10); PP.2401-5, UNIV. MINNESOTA;MED. SCH.; MINNEAPOLIS; 55455; MN; USA (US) Robinson M B et al 'Displacement of DL-[3H]-2-amino-4-phosphonobutanoic acid ([3H]APB) binding with methyl-substituted APB analogs and glutamate agonists' see page 2403; table II ---	1-7
X	MONATSH. CHEM. (MOCMB7,00269247);93; VOL.124 (10); PP.1071-5, UNIV. WIEN;INST. ORG. CHEM.; VIENNA; A-1090; AUSTRIA (AT) Haeusler J 'Synthesis von alpha-Methyl-homocysteinthiolacton' see page 1075 --- -/--	1,5-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1995	26.04.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Pauwels, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HELV. CHIM. ACTA (HCACAV,0018019X);85; VOL.68 (6); PP.1507-18, EIDG. TECH. HOCHSCH.;LAB. ORG. CHEM.; ZURICH; CH-8092; SWITZ. (CH) Aebi J D et al 'Enantioselektive alpha-Alkylierung von Aspargin- and Glutaminsäure über Dilithium enolatocarboxylate von 2-[3-Benzoyl-2-(tert-butyl)-1-methyl-5-oxoimidazolidin-4-yl]essigsäure und 3-[3-Benzoyl-2-(tert-butyl)-1-methyl-5-oxoimidazolidin-4-yl]propionsäure' see page 1517	1-7
X	US,A,4 260 823 (P.J. CASARA) 7 April 1981 see examples 2,6-8	1-7
X	US,A,4 133 964 (B.M. METCALF) 9 January 1979 see examples 1-3,6-10	1-7
X	US,A,2 658 912 (K. PFISTER) 10 November 1953 see column 1, line 5 - line 18	1-7
X	DE,A,28 24 116 (MERCK & CO.) 29 July 1980 see example 8	1-7
X	POL. J. PHARMACOL. PHARM. (PJPPAA,03010244);85; VOL.37 (5); PP.575-84, MED. ACAD.;INST. CLIN. PATHOL.; LUBLIN; 20-090; POL. (PL) Kleinrok Z et al 'Preliminary pharmacological investigation on 38 aminophosphonic acids and their derivatives' see page 576; examples 7,9	1-7
X	NEUROSCI. LETT. (NELED5,03043940);83; VOL.36 (1); PP.75-80, UNIV. CHILE;FAC. MED.; SANTIAGO; CHILE (CL) Berdichevsky E et al 'Kainate, N-methylaspartate and other excitatory amino acids increase calcium influx into rat brain cortex cells in vitro' see page 77; table 1	1-7
X	EP,A,0 418 863 (MERELL DOW PHARMACEUTICALS) 27 March 1991 see claims	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/02690

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The search revealed a large number of highly relevant documents. It is therefore not feasible to make a complete search report. The cited documents are a selection based on the structures and the properties of the examples given in the description. For the same reason the search has been mainly directed to the compounds of described in the examples.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4260823	07-04-81	NONE	
US-A-4133964	09-01-79	US-A- 4190586	26-02-80
US-A-2658912	10-11-53	NONE	
DE-A-2824116	14-12-78	US-A- 4325961	20-04-82
		AT-B- 360509	12-01-81
		AU-B- 518479	01-10-81
		AU-A- 3658678	06-12-79
		CA-A- 1120040	16-03-82
		CH-A- 639639	30-11-83
		FR-A,B 2392958	29-12-78
		GB-A- 1602525	11-11-81
		JP-B- 1001474	11-01-89
		JP-C- 1524826	12-10-89
		JP-A- 54016423	07-02-79
		LU-A- 79750	02-02-79
		NL-A,B,C 7805981	05-12-78
		SE-A- 7806440	02-12-78
		US-A- 4215221	29-07-80
		BE-A- 867702	01-12-78
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EP-A-0418863	27-03-91	US-A- 5095009	10-03-92
		AT-T- 116653	15-01-95
		AU-B- 632362	24-12-92
		AU-A- 6247490	28-03-91
		CA-A- 2025326	20-03-91
		CN-A- 1050387	03-04-91
		DE-D- 69015745	16-02-95
		JP-A- 3130295	04-06-91
		US-A- 5326756	05-07-94